UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,205	04/09/2004	Hong Zhao	213.1152-CIP	3686

20311 7590 01/02/2008

LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
01/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,205	ZHAO ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *20 and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 24, 2007 has been entered.

Election/Restrictions

Claims 20 and 22-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The subject matter of claim 8 directed to SEQ ID NO: 3 is also withdrawn as being a non-elected sequence. Applicant timely traversed the restriction (election) requirement in the reply filed on January 27, 2006.

Specification

Upon further consideration, objection to the specification is withdrawn. The amendment to the specification at pages 11 and 12 by changing the "X" to "M" in the

phosphate group of several structures is accepted as a narrowing amendment to conform to the working examples. Similarly, the rejection of claim 2 for introducing new matter is withdrawn.

Claim Rejections - 35 USC § 112

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites that in SEQ ID NO: 4 n is "any compatible nucleotide". This phrase is indefinite because there is no art recognized meaning for the term "compatible nucleotide" in the context of the claim.

Response to arguments

Applicants note in their remarks that claim 8 has been withdrawn from consideration due to the presence of non-elected SEQ ID NO: 3 and have indicated this status identifier. Since claim 8 contains the elected sequence of SEQ ID NO: 1, it is under examination and not withdrawn; only the subject matter within claim 8 that pertains to SEQ ID NO: 3 is not under consideration.

Claim Rejections - 35 USC § 103

Claims 1-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teng et al. (US 6,887,906) in view of Greenwald et al. (US 6,303,569) and Dandliker et al. (US 5,707,813).

The claimed invention is directed to prodrug compounds comprising an oligonucleotide and one or more polymers, linking moieties and spacers. In specific embodiments the oligonucleotide component is a phosphorothioate and may be an antisense, the linking moiety comprises an aromatic group, the antisense sequence is SEQ ID NO: 1 and the polymer component is a polyalkylene oxide such as polyethylene glycol.

Teng et al. teach compositions of antisense oligonucleotides useful for therapeutic purposes. One of these is a sequence 18 bases in length targeted to bcl-2 and designated as SEQ ID NO: 34, which is identical to instant SEQ ID NO: 1. At column 10 Teng et al. teach that the antisense compounds of the invention can comprise modified linkages such as phosphorothioates. At column 17, lines 58-67 Teng et al. teach that the oligonucleotides of their invention can be provided in prodrug form, an inactive form that is converted to active form within a cell. Teng et al. do not explicitly teach the use of polymeric prodrugs.

Greenwald et al. teach that poor solubility and rapid degradation *in vivo* are recognized problems of some therapeutic agents. One solution to these problems is the use of prodrugs; inactive forms of a drug that are metabolized within the body to form the active agent. The use of prodrugs can allow one to increase the solubility and lifetime of a drug. Greenwald et al. teach polymeric prodrugs illustrated at columns 2-3 as formula I. The prodrugs comprise a polymer region, designated as R_{11}, a linker comprising an aromatic group, a spacer designated as L_2 and a drug component designated as B. At columns 18-19 Greenwald et al. teach that the drug component B includes nucleic acids such as DNA or RNA. At columns 9-10 Greenwald et al. teach

that polyalkylene oxides such as polyethylene glycol are a preferred polymer component of the prodrug and that these polymers have molecular weights in the range of 2000-100000. The polymer component can have a capping structure such as an alkyl group or can comprise the structure shown as figure II, which would produce a bis-prodrug, wherein the two drug components are identical or different.

It was well known in the art at the time of invention to employ alkyl linkers as a component of an oligonucleotide conjugate. For example Dandliker et al. teach that a commercially available reagent can be used to produce an oligonucleotide having a hexylamine at the 5' terminus. This linker allows the skilled artisan to produce a variety of conjugates by attaching different groups to the oligonucleotide through reaction with the primary amine.

It would have been obvious to one of ordinary skill in the art at the time of invention to produce the bcl-2 sequence of Teng et al. in prodrug form as a polymeric prodrug, including a polymeric bis-prodrug, as taught by Greenwald et al. Teng et al. provide a motivation to make the antisense sequence as a prodrug by explicitly suggesting their oligonucleotides be formulated as prodrugs. Greenwald et al. provide a motivation to make polymeric prodrugs by teaching that polymeric prodrugs allow an increase in the solubility and stability of therapeutic agents and explicitly suggest their use with nucleic acid drugs. It is further obvious to use hexylamine linkers as a component of the prodrug because Dandliker et al. teach that the person of ordinary skill in the art would be familiar with the use of such linkers due to the commercial availability of reagents that make such linkers and the extensive use of hexylamine linkers for producing a variety of oligonucleotide conjugates. One of ordinary skill in the

art would have had a reasonable expectation of success in producing a polymeric prodrug of the bcl-2 sequence because Greenwald et al. provide detailed guidance for the synthesis of polymeric prodrugs.

Thus, the invention of claims 1-19 and 21 would have been obvious, as a whole, at the time of invention.

Response to Arguments

As part of their remarks, applicants have requested that the Examiner take administrative notice that chemistry, and particularly the chemistry of nucleotides, is an unpredictable art area. This request is not understood because the rejection of record is not based on an alleged unpredictability of nucleotide chemistry and no reasoning has been provided why such notice is required and why the art would be considered unpredictable.

Applicants traverse the rejection by arguing that the lack of teaching in the Teng reference of polymeric prodrugs is not a minor deficiency that can be overlooked and that in the absence of a teaching in the art about the nature of the linkage between a polymer and an oligonucleotide to provide a prodrug, the ordinary artisan would have had no reasonable expectation of success in making and using any of the claimed compounds.

Applicants are correct that Teng does not teach polymeric prodrugs, however, this lack of teaching has not been treated as a minor deficiency that has been overlooked. The teachings not present in Teng are found in the Greenwald reference.

Applicants argue the Greenwald reference does not remedy the lack in Teng because Greenwald fails to teach or suggest providing an amino-linked separator or tail between the oligonucleotide and the polymer as required by claim 1.

While claim 1 does not specifically recite an amino linked separator or tail, it is assumed that applicants' remarks are referring to the bifunctional spacing groups represented in claim 1 as L_2 and L_3 and illustrated in the structures of claim 21 as a hexylamine attached to the oligonucleotide phosphate. Greenwald et al. teach these spacing groups in the particular embodiment of a prodrug structure that is shown at columns 2-3. In the Greenwald et al. reference the moiety designated as L_2 is a bifunctional linker between the releasable moiety and the drug component.

Applicants further argue that the Dandliker reference is non-analogous art inappropriate for the instant rejection, arguing that Dandliker teaches an oligonucleotide linked to a detectably labeled marker component comprising a fluorophore moiety and does not teach that the marker moiety is releasable from the oligonucleotide. This argument is not persuasive because the Dandliker reference is not relied upon to teach markers that can be released from an oligonucleotide, but to demonstrate that the hexylamine linker illustrated in claim 21 is a commercially available reagent known to those in the art and routinely used in the oligonucleotide art as a spacer moiety.

Applicants additionally argue that the ordinary artisan, who has looked to Greenwald, would have more likely conjugated the releasable linker directly to a nucleic acid base, instead of via an additional linker, noting that figure 12 of Greenwald illustrates PEG conjugated on the amine of the nucleoside. Based on this figure applicants conclude that this can only suggest that a polymer should be conjugated via

the nucleic acid base and fails to teach or suggest utilizing the "tail" structure as recited by the pending claims.

This argument is not persuasive because the teaching of Greenwald is not limited to the structure shown in figure 12 and applicants have presented no reason why those in the art looking to Greenwald would be limited to only the embodiment shown in figure 12. With regard to the tail structure asserted to be recited in the pending claims, it is noted that claim 1 does not specify how the oligonucleotide and moieties L_2 and L_3 are connected, therefore this claim encompasses conjugation via the nucleic acid base. While the structures shown in claim 21 do illustrate conjugation through the terminus of the oligonucleotide, the Dandliker reference provides a teaching of conjugation of a spacer through this position using a commercially available reagent.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
December 20, 2007